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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/582,413 | 10/26/2006 | Toshihiko Ohtomo | 14875-164US1 C1-A0321P-US | 7418 |
| 26161 | 7590 | 12/23/2010 | EXAMINER | |
| FISH & RICHARDSON P.C. (BO) P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022 | | | | DUFFY, BRADLEY |
| ART UNIT | | PAPER NUMBER | | |
| | | 1643 | | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/582,413 | OHTOMO ET AL. |
| | Examiner | Art Unit |
| | BRADLEY DUFFY | 1643 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 October 2010.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 40-42,49,50,54 and 59 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 40-42,49,50,54 and 59 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>4/14/10, 10/15/10</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendment filed October 15, 2010, is acknowledged and has been entered. Claims 55 and 58 have been canceled. Claims 40, 41 and 59 have been amended.
2. Claims 40-42, 49, 50, 54 and 59 are pending and are under examination.

Information Disclosure Statement

3. The references cited in the information disclosure statements filed on April 14, 2010, and October 15, 2010, have been considered. Furthermore, while considered, the Office Actions and Office Action responses cited on these information disclosure statements have been crossed out because these citations clearly do not conform to the information disclosure statement requirements and are not suitable for printing on the issued patent. See MPEP 609.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The rejection of claims 40-42, 49, 50, 54 and 59 under 35 U.S.C. 103(a) as being unpatentable over by WO 2002/033072 A1 (Tsuchiya et al, 2002, IDS filed 5/23/07) as evidenced by US PG PUB 2004/0091475 A1 (Tsuchiya et al, 2004, IDS filed 5/23/07), is maintained. Since WO 2002/033072 A1 is written in Japanese, the page numbers of US 2004/0091475 A1, which is the publication of the national stage entry application of WO 2002/033072 A1, will be cited to evidence the teachings of WO 2002/033072 A1.

As amended, the claims are herein drawn to methods comprising:

- (a) identifying an antibody that binds to mpl receptor;
- (b) providing the antibody's light chain variable region amino acid sequence and heavy chain variable region amino acid sequence; and
- (c) producing an sc(Fv)₂ or covalently linked scFv multimer comprising two or more copies of said light chain variable region sequence of (b) and two or more copies of said heavy chain variable region sequence of (b), linked via linkers,
- (d) testing the sc(Fv)₂ or covalently linked scFv multimer for said TPO-like agonistic activity (TPO)-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor,
- (e) demonstrating that the sc(Fv)₂ or covalently linked scFv multimer binds to

mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b). The claims are further drawn to the antibody being human or humanized, or wherein the sequence of the sc(Fv)2 comprises, in order: the heavy chain variable region sequence, a first linker sequence, the light chain variable region sequence, a second linker sequence, the heavy chain variable region sequence, a third linker sequence, and the light chain variable region sequence: and

(f) selecting the sc(Fv)₂ or covalently linked scFv multimer.

Starting at page 6 of the response filed October 15, 2010, Applicant has traversed this ground of rejection.

In this response, Applicant has argued that WO 2002/033072 A1 does not supply either a motivation to carry out the presently claimed methods or an expectation of success upon doing so because “while WO 2002/033072 A1 does generally disclose the idea of making single chain polypeptides containing two or more H chain V regions and two or more L chain V regions (see, e.g., [0013] of US 2004/0091475 A1)), the only modified anti-mpl antibodies actually made and tested in the reference’s Examples are scFv monomers and non-covalently linked multimers of scFv, i.e., diabodies, triabodies and tetrabodies” and “[t]here is no reason whatsoever to assume that another form of modified antibody-one that the WO 20002/033072 A1 researchers did not even bother to make---would exhibit even greater activity than the diabodies of Examples 7 and 8. Accordingly, until Applicants carried out their experiments, there could not have been an expectation that the presently claimed methods would be successful”.

In response, these arguments are not found persuasive because the rejection is not based on one of skill in the art having the assumption that sc(Fv)₂ or covalently linked scFv antibodies which bind to mpl receptor would exhibit even greater activity than the corresponding diabodies. In this case, the intended use is for selecting a scFv

multimer with thrombopoietin (TPO)-like agonistic activity, wherein the TPO-like agonistic activity is stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor, and one would have expected success in selecting a scFv multimer with thrombopoietin (TPO)-like agonistic activity based on the art of record. In this case, since the parent antibody was shown to have TPO-like agonistic activity in stimulating cell proliferation by activating myeloproliferative leukemia virus oncogene (mpl) receptor, one of skill in the art would have expected that both the diabodies and sc(Fv)₂ or covalently linked scFv antibodies produced from this parent also would have such an activity and would have expected success in selecting a scFv multimer with thrombopoietin (TPO)-like agonistic activity.

Secondly, Applicant has argued that because WO 2002/003072 A1 discloses production of a covalently linked scFv dimer of MABL-2 which has lower activity in inducing apoptosis than the corresponding diabody “one of ordinary skill would generally expect the same to be true of other antibodies that act on other cell-surface molecules” and that this disclosure teaches away from the claimed invention.

In response, it appears that Applicant’s representative is arguing that one of skill in the art would have considered that an scFv multimer produced from an antibody which binds to mpl receptor having higher thrombopoietin (TPO)-like agonistic activity than the corresponding diabody is an *unexpected result*.

First, this argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. As set forth in MPEP 716.01:

Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of **unexpected results**, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) (“It is well settled that unexpected results must be established by factual evidence.”) See also *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991). The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA

1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.

Accordingly, while the arguments of counsel about the expectations of one of ordinary skill are noted, they were not found persuasive as no affidavit or declaration include statements regarding the expectations of one of ordinary skill have been submitted. In further response, as has been set forth in further detail in the action mailed June 25, 2009 starting at page 12, it is noted in the art that "antibodies can have an diverse number of different and unpredictable activities depending on the epitope bound as well as the particular immunoglobulin subclass, i.e., IgM, IgG, IgE, etc of the antibody such as inhibiting cell proliferation, increasing cell proliferation, activating antibody dependent cellular cytotoxicity, mediating complement dependent cytotoxicity, etc. For example, it is recognized in the art that depending on the epitope bound by an antibody on the antigen the antibody binds that some antibodies can inhibit cell growth while some antibodies can actually accelerate growth (see e.g., Stancovski et al (PNAS, 88: 8691- 8695, 1991 (page 8693, column 1)). Notably, Jiang et al. (J. Biol. Chem. 2005 Feb 11; 280 (6): 4656-4662) teach that the reason that antibodies which bind the same antigen can have opposite effects is because it is well known that different biological effects are associated with epitope specificity of the antibodies (see entire document, particularly page 4656, column 2). Accordingly, since it is established in the art that there is a high degree of unpredictability in determining the activities of antibodies that bind any given antigen, one of skill in the art would also recognize that whether any particular activity of an antibody was increased as compared to some diabody by producing an sc(Fv)2 from a parental antibody would also be highly unpredictable". Even in the current specification at page 27 it is set forth that "since the sc(Fv)2 which is

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linked by a linker is more stable, there is a **possibility**¹ that it can confer a higher activity as compared with a non-covalent diabody". In further response, as evidence to the weight one of skill in the art would have given the results obtained relating to the MABL-2 antibody, it is submitted that one of skill in the art understood that the activity of any given construct was dependent on both the structure of the antibody and the structure of the receptor. For example, according to Hudson et al (JIM, 231:177-189, 1999), the ability of recombinant antibody constructs to cross-link receptors "will obviously depend of flexibility between the Fv molecules and the orientation of the antigen binding sites, as well as the structure of the receptor" (see page 185). Accordingly, it is submitted that one of skill in the art would not have been able to draw any conclusion about the function of a genus of sc(Fv)₂ or covalently linked scFv antibodies which bind to mpl receptor based on the results obtained with an antibody of different structure which binds to a different receptor.

On the contrary, it is in part because one of skill in the art recognized that there is a high degree of unpredictability in determining the activities of antibodies that bind any given antigen that one of skill in the art would have been motivated to make sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv antibodies which bind to mpl such as disulfide linked diabodies along with the diabodies made in the prior art and test them for thrombopoietin (TPO)-like agonistic activity. In this case, because one of skill in the art could not predict the activity of sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv antibodies which bind to mpl, one of skill in the art would have been motivated to make such constructs and test them for TPO-like agonistic stimulation of cell proliferation to determine if they had higher TPO agonist action as compared to the corresponding diabody or original antibody because WO 2002/033072 A1 clearly teaches a preference for antibodies having higher TPO agonist action as compared to another antibody having TPO agonist action. Accordingly, based on the teachings of WO 2002/033072 A1 it is maintained that it would have been obvious to make and test sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv

¹ Emphasis added

antibodies which bind to mpl such as disulfide linked diabodies for TPO agonist action. Then because the sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv antibodies which bind to mpl such as disulfide linked diabodies suggested by WO 2002/033072 A1 are materially and structurally indistinguishable from the claimed sc(Fv)₂ antibodies which bind to mpl and other claimed covalently linked scFv antibodies which bind to mpl, it is also reasonably expected that one of skill in the art would have had success in those tests demonstrating that the sc(Fv)₂ or covalently linked scFv multimer binds to mpl receptor and exhibits said TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b).

Notably, Applicant has not argued or otherwise demonstrated that the sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv antibodies taught in WO 2002/033072 A1 are materially or structurally different than the claimed sc(Fv)₂ antibodies which bind to mpl and other claimed covalently linked scFv antibodies which bind to mpl, so it is submitted that the sc(Fv)₂ antibodies which bind to mpl and other covalently linked scFv antibodies taught in WO 2002/033072 A1 would inherently have TPO-like agonistic activity at a level that is (i) greater than the level at which the antibody of (a) exhibits the same activity and (ii) greater than the level at which a diabody exhibits the same activity, the diabody consisting of two identical, non-covalently associated single-chain polypeptides, each of which consists of one copy of said light chain variable region sequence of (b) linked via a linker to one copy of said heavy chain variable region sequence of (b). Applicant is reminded that products of identical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Once again it is not a question of whether one of skill in the art would have reasonably expected the sc(Fv)₂ antibodies which bind to mpl and other covalently

linked scFv antibodies which bind to mpl to have higher TPO agonist action as compared to the corresponding diabody and parental antibody. The prior art taught motivations to test and select recombinant antibody constructs with the highest TPO-like agonistic activity and the methods taught by the prior art would have lead to success in one of skill in the art practicing methods encompassed by the claims.

Therefore, for these reasons and the reasons previously set forth, and after careful and complete consideration of Applicant's response, this rejection is maintained.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
December 13, 2010